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Association between *STAT3* rs1053004 polymorphism and cancer risk: a meta-analysis

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ABSTRACT

Several studies examined the relationship between *STAT3* rs1053004 polymorphism and the risk of some human cancers, but the findings remains inconclusive. To evaluate the impact of *STAT3* rs1053004 on cancer risk, we conducted a meta-analysis of all available studies including 4,605 cancer cases and 5,248 controls. Eligible studies were identified by searching PubMed, Web of Science, Scopus, and Google scholar databases. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated in codominant, dominant, recessive, overdominant, and allele models to quantitatively estimate the association. The overall findings showed no significant association between *STAT3* rs1053004 polymorphism and cancer risk in codominant, dominant, recessive, overdominant, and allele inheritance model tested. In summary, the findings of this meta-analysis indicates no significant association between *STAT3* rs1053004 polymorphism and cancer development. Larger and well-designed studies are necessary to estimate this association in detail.

Keywords: STAT3; Cancer; Meta-analysis; Susceptibility

INTRODUCTION

Cancer, one of the leading cause of morbidity and mortality, is a public health problem worldwide [1]. Approximately 8.2 million cancer-related deaths and 14.1 million new cancer cases occurred in 2012 worldwide [2]. Mounting evidences indicate that multiple factors contribute to the etiology and pathogenesis of cancer [3, 4].

STAT3 is oncogenic downstream mediators of the Janus kinase/Signal transducer and activator of transcription (JAK/STAT) pathway [5]. The human *STAT3* gene has been mapped to long arm of chromosome 17 (17q21) [6]. STAT3, a 1128 amino acid protein with a molecular weight of 93 kDa, is involved in regulating cellular differentiation, proliferation, and survival [7]. Phosphorylation of Tyr_{705} by upstream kinases is the key mechanism of activation of STAT3, though residue Ser_{727} can similarly be phosphorylated. Also, unphosphorylated STAT3 is transcriptionally active and its activity is regulated by posttranslational modifications including acetylation, methylation or ubiquitination [8].

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STAT3 is a polymorphic gene and several studies have inspected the association between single-nucleotide polymorphisms (SNPs) in the *STAT3* gene and risk of cancer in various populations [9]. The results of a meta-analysis performed by Yan et al [9] indicated that *STAT3* rs12949918 and rs744166 polymorphisms significantly decreased the risk of cancer, but rs2293152, rs4796793, and rs6503695 polymorphisms were not associated with cancer risk. In addition, several studies investigated the impact of rs1053004 polymorphism of *STAT3* on cancer risk [10-16], however the results were controversial. So, for the first time, in this study, we conducted a meta-analysis to evaluate the association between the rs1053004 polymorphism gene and cancer risk.

MATERIALS AND METHODS

Literature search: A comprehensive literature searches in Web of Science, PubMed, Scopus, as well as Google Scholar databases was conducted for all articles regarding the impact of STAT3 rs1053004 polymorphism on cancer risk published up to June 02, 2018. The search term was "cancer or carcinoma or tumor or neoplasms" and "STAT3" and "polymorphism or mutation or variant or rs1053004". Figure 1 summarized the process of identifying eligible studies. Relevant studies included the meta-analysis if they met the following inclusion criteria: 1) Original case-control studies that evaluated the *STAT3* polymorphisms and cancer risk; 2) studies provided necessary information of the genotype frequencies of *STAT3* rs1053004 variant in both cases and controls. The exclusion criteria were: 1) conference abstract, case reports, reviews, duplication data; 2) insufficient genotype information provided.

Data extraction: Data extraction was achieved by authors. The following data were collected from each study such as the first author's name, publication year, country, ethnicity, cancer type, genotyping methods of *STAT3* rs1053004 polymorphism, the sample size, the genotype and allele frequencies of cases and controls (Table 1).

Statistical analysis: All analyses were performed using Revman 5.3 software (Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014) and *STATA* 14.1 software (Stata Corporation, College Station, TX, USA). The Hardy–Weinberg equilibrium (HWE) were calculated by the chi-square test in control groups, in order to verify the representativeness of the study population. The relationship between rs1053004 polymorphism and cancer risk was estimated by pooled odds ratios (ORs) and their 95% confidence intervals (CIs). Pooled ORs and their 95% CIs for codominant CT *vs* TT and CC *vs* TT), dominant (CT+CC *vs* TT), recessive (CC *vs* CT+TT), overdominant (CT *vs* CC+TT) and the allelic comparison (C *vs* T) genetic inheritance models were calculated. The significance of the pooled OR was assessed by the Z-test, and $P<0.05$ was considered to be statistically significant. The choice of using fixed or random effects model was determined by the results of the between-study heterogeneity test, which was measured using the Q test and I^2 statistic. If the test result was $I^2 \geq 50\%$ or $P_Q < 0.1$, indicating the presence of heterogeneity, the random effect model was selected; otherwise, the fixed-effects model was chosen.

Begg's funnel plot was conducted under all inheritance models to evaluate the publication bias and the asymmetric plots implied potential publication bias. The degree of funnel plot asymmetry was measured using Egger's test; p value less than 0.05 was considered significant publication bias. Sensitivity analysis was conducted to measure the effect by ignoring a single study at a time.

RESULTS

The process of literature retrieval and selection are shown in Figure 1. Totally seven case-

control studies including 4,605 cancer cases and 5,248 controls which met the inclusion criteria were included in our meta-analyses. The characteristics and relevant data of the included studies are summarized in Table 1.

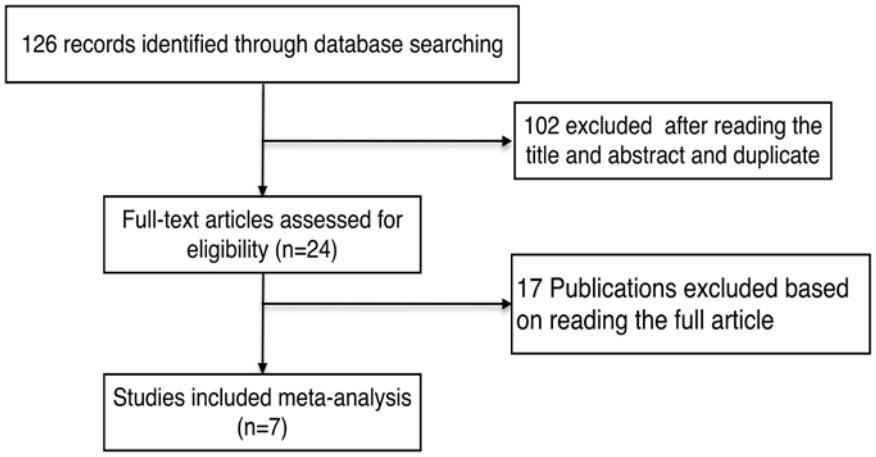

Figure 1: Flow chart illustrates the detailed study selection process of this meta-analysis

Table 1: Characteristics of the studies eligible for meta-analysis

Author	Year	Country	Ethnicity	Cancer type	Source of control	Method	Case/ control	Cases			Controls			HWE
								TT	CT	CC	TT	CT	CC	
Chanthra	2015	Thailand	Asian	HC	HB	TaqMan	211/206	55	107	49	77	99	30	0.841
Fatemipour	2017	Iran	Asian	HC	HB	TaqMan	33/50	10	5	18	32	14	4	0.193
Jiang	2011	China	Asian	NSCLC	HB	TaqMan	326/432	148	136	42	173	205	54	0.574
Li	2018	China	Asian	HC	HB	TaqMan	187/169	82	82	23	88	76	5	0.016
Xie	2013	China	Asian	HC	HB	TaqMan	1009/995	411	458	140	453	400	142	0.001
Zhou	2016	China	Asian	GC	HB	TaqMan	1125/1221	445	549	131	432	614	175	0.067
Zhu	2016	China	Asian	PC	HB	TaqMan	1714/2175	759	761	194	874	991	310	0.283

HB, hospital based; HC, hepatocellular carcinoma; GC, gastric cancer; PC, pancreatic cancer; NSCLC, non-small cell lung cancer; HWE, Hardy-Weinberg equilibrium

In the current meta-analysis of 7 eligible studies, the results did not support an association between rs1053004 variant and cancer risk in the overall population in codominant, dominant, recessive, overdominant and allele genetic model (Fig. 2 and Table 2).

Heterogeneity among the studies incorporated in the meta-analysis is shown in Table 2. The findings showed that heterogeneity exist in overall comparisons analysis. The funnel plot is presented in Figure 2. The potential publication bias was evaluated using a Begg's and Egger's tests. The shape of funnel plots and the Begg's and the Egger's tests showed that no publication bias exist in heterozygous codominant, recessive, and overdominant inheritance models (Table 2, Fig. 3).

Table 2: The pooled ORs and 95%CIs for the association between *STAT3* rs1053004 polymorphism and cancer susceptibility

Genetic model	Association test			Heterogeneity			Egger's test P-value	Begg's test P-value
	OR (95%CI)	Z	p	$\chi 2$	I^2(%)	P		
CT *vs* TT	1.01 (0.85-1.20)	0.12	0.91	17.39	65	0.008	0.442	0.293
CC *vs* TT	1.39 (0.91-2.11)	1.52	0.13	47.77	87	<0.00001	0.004	0.004
CT+CC *vs* TT	1.11 (0.88-1.39)	0.90	0.37	33.92	82	<0.00001	0.066	0.051
CC *vs* CT+TT	1.31 (0.91-1.89)	1.46	0.14	40.85	85	<0.00001	0.001	0.002
CT *vs* CC+TT	0.99 (0.87-1.12)	0.22	0.83	11.12	46	0.08	0.540	0.881
C *vs* T	1.18 (0.96-1.46)	1.55	0.12	57.76	90	<0.00001	0.011	0.011

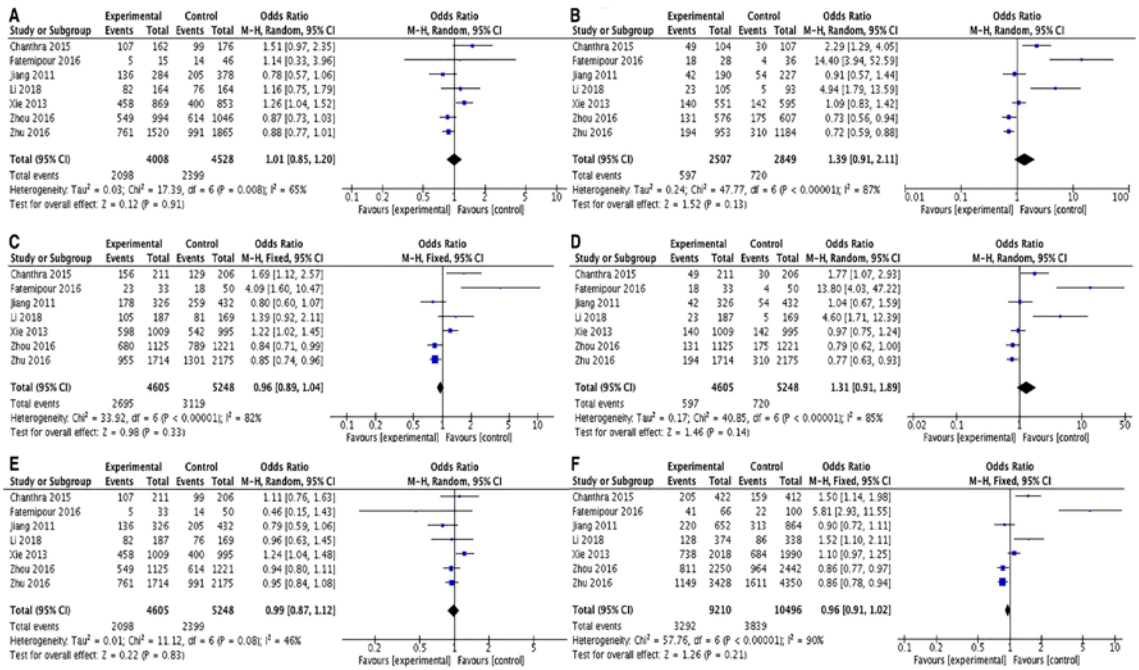

Figure 2: The pooled ORs and 95%CIs for the association between *STAT3* rs1053004 polymorphism and cancer susceptibility. The forest plot for relationship between *STAT3* rs1053004 polymorphism and cancer susceptibility for CT *vs* TT (**A**), CC *vs* TT (**B**), CT+CC *vs* TT (**C**), CC *vs* CT+TT (**D**), CT *vs* CC+TT (**E**), and C *vs* T (**F**).

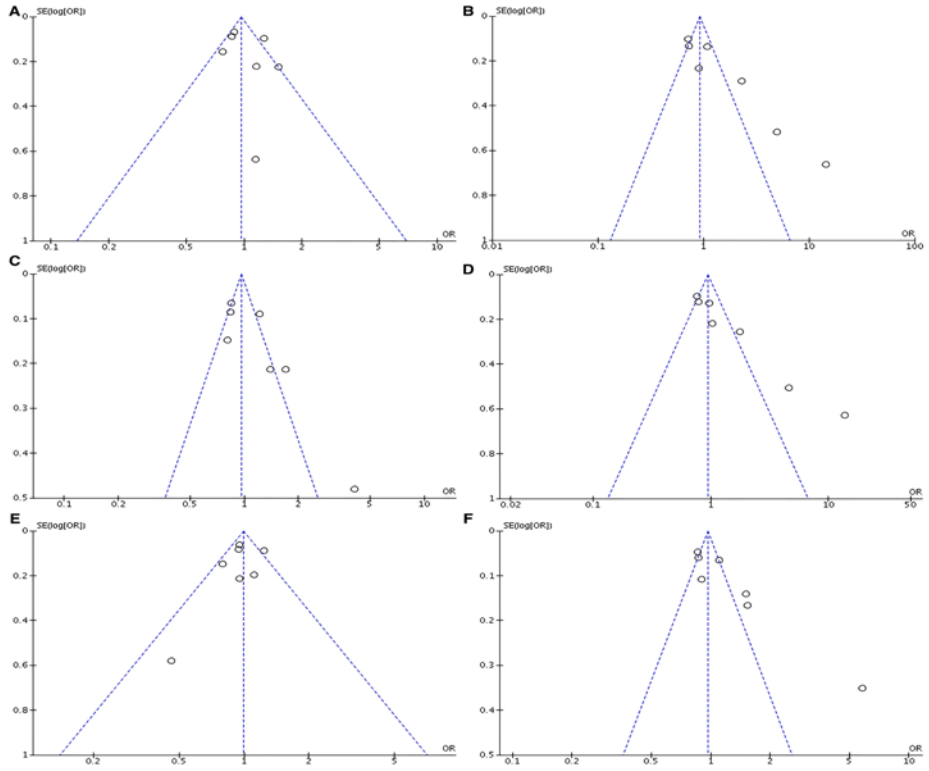

Figure 3: The funnel plot for the test of publication bias. The funnel plot for CT *vs* TT (**A**), CC *vs* TT (**B**), CT+CC *vs* TT (**C**), CC *vs* CT+TT (**D**), CT *vs* CC+TT (**E**), and C *vs* T (**F**).

Sensitive analysis was conducted though deleting each study one by one, and the results indicated that the pooled ORs were not considerably altered, proposing the stability of our meta-analysis.

DISCUSSION

The JAK/STAT cascade is an important signal transduction pathway in cytokine and growth factor signaling, regulating several cellular processes including cell proliferation, differentiation, migration and survival [17]. STAT3 is basically activated by phosphorylation of the conserved tyrosine residue at position 750 (Tyr_{705}), which leads to dimerization and translocation to the nucleus through interactions with importins and activate transcription of its target genes [18, 19]. Constitutive activation of JAK/STAT signaling pathway is well-known in cancers [17, 20, 21]. Preceding studies inspected the possible relationship between rs1053004 polymorphism and risk of various cancer including hepatocellular carcinoma [10-13], gastric cancer [14], pancreatic cancer [15], and non-small cell lung cancer [16]. The data were controversial. Consequently, we performed a meta-analysis of all available case–control studies to find out the exact role of rs1053004 polymorphism on cancer risk. The outcomes of our meta-analysis on seven case-control studies including 4,605 cancer cases and 5,248 controls proposed no significant association between rs1053004 variant and cancer risk.

There are some limitations that should be addressed. First, high heterogeneity was observed in some of our pooled results, which might have negative impact on our conclusions. Second, in this study, all subjects are of Asian descent, so statistical power for analyses in other ethnicities is limited. Third, the characteristics of included studies, such as age and sex, were varied and might affect the results of meta-analysis.

To the best of our knowledge, our study is the first comprehensive meta-analysis failed to find any significant association between rs1053004 polymorphism and cancer risk. Further studies in others ethnic groups are required to give more comprehensive understanding the exact role of rs1053004 polymorphism on cancer risk.

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Conflict of Interest: The authors have no conflict of interest to declare.

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